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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/030,803	04/09/2002	Thomas Kissel	99/074 MED	5609
38263	7590	07/31/2007		
PROPAT, L.L.C. 425-C SOUTH SHARON AMITY ROAD CHARLOTTE, NC 28211-2841			EXAMINER FUBARA, BLESSING M	
			ART UNIT 1618	PAPER NUMBER
			MAIL DATE 07/31/2007	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/030,803

Applicant(s)

KISSEL ET AL.

Examiner

Blessing M. Fubara

Art Unit

1618

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 April 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3,6,8,10-13 and 19-24 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3,6,8,10-13 and 19-24 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

Art Unit: 1618

DETAILED ACTION

Examiner acknowledges receipt of request for extension of time; request for continued examination filed under 37 CFR 1.114, Exhibit I, amendment and remarks, all filed 4/23/07.

Claims 14 and 15 are canceled without prejudice. Claims 1-3, 6, 8, 10-13 and 19-24 are pending.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/23/07 has been entered.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-3, 6, 8, 10-13 and 19-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled

Art Unit: 1618

in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is new matter rejection.

The specification as filed does not provide support for "further comprising a moiety $[A]_w$." Applicant points to page 6, lines 1 through 16 as providing support. However, the expression $[A]_w$ is not found.

The specification does not also provide support for $-O(CH_2)_pC(O)-$ with $p = 1$ and 3-10 basically excluding when $p = 2$. The specification at page 3 (amended sheet) provides support for $p = 1-10$ and 1 to 3 and not $p = 1$ and 3-10 or $p = 1$ and 3.

The specification does not also provide support for a compound where the hydrophilic non-ionic polymer is a 13-, 18- and 24-arm.

The specification does not provide support for 5000 to 10 000 000 g/mole. Support is however provided for 5000 to 50 000 and 100 to 10 000 000 g/mole. See replacement page 3, line 7.

The rejection above may be overcome by removing the new matter from the claims.

Response to Arguments

4. Applicant's arguments filed 4/23/07 have been fully considered but they are not persuasive.

a) Applicant argues that the specification at page 5, lines 15-24 "clearly indicate that "B" advantageously includes a group $[A]_w$ and that "A" is further defined as an anion on page 6, lines 15 and 16 such that applicant had possession of the invention claimed. b)

Applicant also states that the as filed specification at page 3, line 5 provides support for p

Art Unit: 1618

= 1 and 3-10 and further that p may be 3 and that the skilled artisan “would consider the lower end points of 1 and 3 and upper end point of 10 to be expressly supported by the discussion in the original disclosure.” c) Applicant also argues that the as filed specification supports molecular weight of 5,000 g/mole as described on page 2, line 20. d) Applicant states that the original specification at page 24 and Example 1 describe a 20-arm.

Response:

Regarding a), it is noted that B is defined as $-\text{[CH}_2\text{CH}_2\text{N}^{(2+)}(\text{R}^2)_x\text{H[A]}_w\text{]}$, so that $[\text{A}]_w$ is part of the structure for “B” (page 5, lines 15-20 and page 6, lines 15 and 16) and does not further comprise $[\text{A}]_w$. The specification reference cited by applicant does not contain any mention of “advantageously” including $[\text{A}]_w$. Regarding b) it is noted that page 3, line 5 supports a range for what p can be and there is no support in the original specification for single points for p at 1 and 3. Regarding c), it is noted that applicant in the remarks acknowledges a range and not a single point of 5,000 g/mole, the specification does not provide support for single molecular weight point of 5,000 g/mole. Contrary to applicant’s argument, page 2 describes molecular weight ranges and no single molecular weight is described in the specification, and specifically, line 20 at page 2 discloses a molecular weight range of 5,000 to 50,000 g/mole and not 5,000 to 10,000,000 g/mole recited in the claim and argued for by applicant. Regarding d), it is noted that $[\text{PEI}/(\text{PEG})_{20}]$ does not state that 20 in the $[\text{PEI}/(\text{PEG})_{20}]$ represents 20 PEG arms. Furthermore, the original specification does not envision the recitation of 13, 18, and 24 arm PEG. A 4-arm and 8-arm species are disclosed throughout the specification and applicant has not pointed to where in the specification the support for 13-, 18- and 24-arm may be found.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 1-3, 6, 8, 23 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Yokomichi et al. (US 5,204,196 cited by applicants on form PTO-1449).

Yokomichi discloses PEG-X-PEI block copolymer (abstract; column 1, lines 34-46); PEG is the hydrophilic moiety having an average molecular weight of 550, which in the example 1 can go to a polymer having average polymerization degree of 11.8 and polyethyleneimine having average molecular weight of about 1300 and a polymerization degree of about 30 (Example 1). The molecular weight of PEI would be the degree of polymerization multiplied by the initial molecular weight of 1300, which would average to about 39000 to meet the limitations of the recited molecular weight for PEI. The molecular weight of the PEG would be the degree of polymerization multiplied by the initial molecular weight of 550, which would average to about 6490. Yokomichi discloses the copolymer of PEG and PEI. Furthermore, example 1 specifically adds sodium hydroxide to the solution of the PEI. The hydroxide ion meets the limitation of A- now recited in the claims. Surfactant in the context of claim 24 is a block copolymer of the nature disclosed by Yokomichi because as gleaned from the specification at

Art Unit: 1618

page 11, lines 16 and 17, the block copolymers are surface active substances that are used as surfactants. Yokomichi thus meets the limitations of the claims.

Response to Arguments

7. Applicant's arguments filed 4/23/07 have been fully considered but they are not persuasive.

Applicant argues that Yokomichi does not teach or suggest the recited balance of charges in the compounds synthesized and does not provide guidance to the skilled artisan as to how the balance the charges because i) higher ratio of ethyleneimine or polyethyleneimine than that indicated as used (shown on page 14 of the remarks) will introduce positive charges in the polymer since the number of positive charges depends on the amount of nitrogen compound added and addition of unknown amount of sodium hydroxide as disclosed by Yokomichi would not be sufficient as "it might be too much thus creating a net negative charge on the molecule synthesized or to less leaving some positive charges on the molecule;" ii) sodium hydroxide in Yokomichi is not used to obtain polyethyleneimine polyethylene glycol copolymer where the two moieties are connected via a diurethane linker that comes from the diisocyanate; iii) the copolymer synthesized in example 1 of Yokomichi is precipitated with "an amount of LiClO_4 such that the final concentration of LiClO_4 in the copolymer/salt composition is 18.6 percent by weight for the six polymer/salt composition in Example 3)" and that the solvent used during polymerization seems to influence the overall charge and conductivity

Art Unit: 1618

characteristics of the polymer; iv) Yokomichi does not teach a minimum molecular weight of 5,000 g/mole.

Response:

The arguments presented in i) through iii) have to do with how the compound is prepared and/or the method of preparing the composition claimed. The claims rejected over Yokomichi are directed to compound/product/composition, these claims are neither process claims nor product-by-process claims. Applicant acknowledges in the arguments that Yokomichi discloses the compound/product and not the process of making the product or the effect of some of the components within the product. Since the claims rejected are directed to product/compound, the process of making the product does not make the product patentable over the product of the prior art. Regarding iv) is noted that the starting molecular weight is 550 and a DP of 11.8 would take to 6490 according to the equation below and as described above. While applicant disputes the computation, applicant has not disputed the equation below.

Specifically, polymerization degree or degree of polymerization DP is

$$DP = \frac{M_t}{M_0}$$

where M_t = molecular weight at time t and M_0 = molecular weight of one monomeric unit.

The monomeric unit of PEO in Example 1 has a molecular weight of 550 and a DP of 100 would mean that the average molecular weight of the PEO polymer would be 55000. However, the DP in Example 1 is disclosed to be 11.8, which will mean that the molecular weight of the PEO/PEG would be 6490. In both cases, the molecular weight of the PEO/PEG meets the limitation of 5000 to 10 000 000 since 55000 or 6490 would touch a point within the

Art Unit: 1618

recited range. It appears that the '196 patent would mean that the molecular weight of the PEO should not exceed 55000 in order to not undermine the conductivity of the polymer if the initial weight of the PEO/PEG is 550. It is also note worthy that the '196 patent, in that text referred to by the applicant, does not particularly disclose the initial molecular weight of the PEO/PEG.

8. Claims 1-3, 6, 8, 10-13, 19 and 24 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 98/59064, cited by applicants on form PTO-1449 and the specification which is the same as US 2001/0005717 to Wagner as pointed out by applicant. Therefore, Claims 1-3, 6, 8, 10-13, 19 and 24 are rejected under 35 U.S.C. 102(e) as being anticipated Wagner et al. (US 2001/0005717).

WO 98/59064 discloses DNA complexes with PEG-PEI conjugate copolymer (English abstract; Examples 1-3), methoxy-succinimidyl propionate PEG (M-SPA-PEG) reacts with the imine (Example 2); the molecular weights of the PEG and PEI meet the limitations of the recited molecular weight (Example 2). The DNA is contacted with the complex of PEG and PEI (Examples 1 and 2). The WO publication and the English equivalent of the WO publication meet the limitations of the claims. Methoxy-succinimidyl propionate (Example 2) is anionic and complex union with PEG stabilizes PEI. Water, which provides hydroxyl groups, which could also meet the limitation of anion. Surfactant in the context of claim 24 is a block copolymer of the nature disclosed by Wagner because as gleaned from the specification at page 11, lines 16 and 17, the block copolymers are surface-active substances that are used as surfactants.

Response to Arguments

9. Applicant's arguments filed 4/23/07 have been fully considered but they are not persuasive.

Applicant states that m-PEG-SPA is methoxy-polyethylene glycol succinimidyl-propionate and not the methoxy-succinimidyl-propionate that Examiner stated.

Applicant argues that Wagner "does not teach or suggest the recited balance of charges in the compound synthesized" because the reaction mechanism dictates that the methoxy-polyethylene glycol succinimidyl-propionate (m-PEG-SPA) will not conserve the anionic character. Applicant further argues that it is wrong to state that the hydroxyl ions in water balance positive charges of the compound because water at neutral pH has equal number of hydroxyl ions and protons/hydrogen ions and the very small amounts of the negative ions cannot equal the positive charge in the compound.

Response:

Examiner respectfully points to paragraph 7, last line, of the Office action of 11/20/06, where it is stated, "methoxy-succinimidyl propionate PEG (M-SPA-PEG)" and the M-SPA-PEG is specifically named in Example 3, paragraph [0095] of Wagner, US 2001/0005717 and Examiner is not clear why what has been disclosed in Wagner, US 2001/0005717 as M-SPA-PEG is interpreted by applicant as m-PEG-SPA. Regarding the methoxy-polyethylene glycol succinimidyl-propionate (m-PEG-SPA) and its inability to stabilize anionic character, it is noted that the claim 1 is a compound/product claim and not a method of preparing the compound or product by process claim; and secondly, Example 3 specifically uses "methoxy-succinimidyl

Art Unit: 1618

propionate PEG (M-SPA-PEG)” and not methoxy-polyethylene glycol succinimidyl-propionate (m-PEG-SPA). Examiner is unable to locate where it was said that the negative hydroxyl ions are capable of balancing the charge of the compound. However, *aguendo*, the charge on a molecule is not related to the size of the molecule, because, it is known in the art that drug molecules such as diclofenac sodium has the small sodium ion associated with the much larger diclofenac molecule. Further, the claims are product/compound claims and not method of balancing charges on the compound. The article submitted as **Exhibit I**, “Development of Pegylated Interferons for the Treatment of Chronic Hepatitis C” by Kozlowski et al. in *BioDrugs* 2001: 15(7); 419-429, does not overcome the rejections and it is also noted that the subject matter of the claims is not the pegylation of interferons or pegylated interferons.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

Art Unit: 1618

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 10-13 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yokomichi et al. (US 5,204,196 cited by applicants on form PTO-1449) in view of Ogris et al. ("PEGylated DNA/transferrin-PEI-complexes: reduced interaction with blood components, extended circulation in blood and potential for systemic gene delivery" in **Gene Therapy** Volume 6, Issue 4 , April 1999, Pages 595-605).

13. Yokomichi discloses PEG-X-PEI block copolymer (abstract; column 1, lines 34-46); PEG is the hydrophilic moiety having an average molecular weight of 550, which in the example 1 can go to a polymer having average polymerization degree of 11.8 and polyethyleneimine having average molecular weight of about 1300 and a polymerization degree of about 30 (Example 1). The molecular weight of PEI would be the degree of polymerization multiplied by the initial molecular weight of 1300, which would average to about 39000 to meet the limitations of the recited molecular weight for PEI. The molecular weight of the PEG would be the degree of polymerization multiplied by the initial molecular weight of 550, which would average to about 6490. Yokomichi discloses the copolymer of PEG and PEI. Furthermore, example 1 specifically adds sodium hydroxide to the solution of the PEI. The hydroxide ion meets the limitation of A- now recited in the claims. Yokomichi does not disclose a complex of DNA with the copolymer. However, Ogris discloses that the complexes can be formed between DNA and PEI and PEG and the complex is formed by contacting the DNA with PEI and PEG (abstract). According to Ogris, pegylation of the complexes reduces plasma protein binding and erythrocyte aggregation, the pegylated complex mediated reporter gene transfer to tumor without

Art Unit: 1618

significant toxicity. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare pegylated DNA complex with PEI with the expectation that therapy with the pegylated DNA complex would reduce toxicity while reducing protein binding and erythrocyte aggregation.

Response to Arguments

14. Applicant's arguments filed 4/23/07 have been fully considered but they are not persuasive.

Art Unit: 1618

Applicant argues that Yokomichi and Ogris, considered alone or in combination, fail to teach or suggest (i) polyethylene glycols having a molecular weight equal to higher than 5,000 g/mole and (ii) polyethyleneimines comprising a moiety $[A^+]_w$ where $[A^+]$ is an equivalent of an anion and w is an integer selected to balance the positive charges in the polyethyleneimine (PEI).” Applicant further argues that the pegylation of DNA-charged polyethyleneimine would produce compounds that are different from the compounds of the invention since a complex of DNA and polyethyleneimine is pegylated instead of pegylation of free polyethylene.

Response:

Firstly, claim 10 does not recite polyethylene glycol but recites generic hydrophilic polymer. Yokomichi discloses polyethylene glycol that is a specific hydrophilic polymer and the molecular weight of the PEG is computed to be 6490 from an initial molecular weight of 550 (M_0) having a degree of polymerization (DP), so that using the relationship below

$$DP = \frac{M_t}{M_0}$$

a molecular weight M_t is 6490, which is greater than 5,000 g/mole. Ogris is relied upon for teaching that complexes can be formed between DNA and PEI and PEG by contacting the DNA with PEI and PEG. Claim 10 is directed to complexing DNA with a compound where the complexation is carried out by contacting the DNA with the polymer $A(-X-B)_n$. Ogris discloses a method where DNA is contacted with PEI and PEG and renders obvious the claimed invention in that DNA as thought by Ogris can also be contacted with a polymer that comprises

Art Unit: 1618

PEG and PEI of the type taught by Yokomichi. Claim 10 is not directed to pegylation of PEG or PEI or DNA as applicant argues.

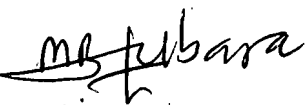
No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Blessing M. Fubara whose telephone number is (571) 272-0594. The examiner can normally be reached on 7 a.m. to 5:30 p.m. (Monday to Thursday).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Blessing Fubara
Patent Examiner
Tech. Center 1600

A handwritten signature in black ink, appearing to read "mfubara", is written over the printed name "Blessing Fubara".